Remarks

Amendments to the Claims

Claims 38, 78, 86, 98, 99, 101, and 102 are amended to correct clerical errors. The amendments do not add new matter or require a new search.

Rejection Under 35 U.S.C. § 112 ¶ 1

Claims 38, 78-90, and 98-103 stand rejected under 35 U.S.C. § 112 ¶ 1 as insufficiently described. Applicants respectfully traverse the rejection.

As an initial matter, on page 3, lines 10-13, the Final Office Action states that "[a]ppropriately draft claim language directed toward SEQ ID NO:120 would be acceptable (i.e., an expression cassette comprising a polynucleotide sequence encoding a codon-optimized modified HIV-1 Env glycoprotein comprising SEQ ID NO:120)." SEQ ID NO:120 is a polynucleotide sequence which encodes an Env polypeptide. The polynucleotide sequence is codon-optimized, not the Env polypeptide. In addition, claims 100 and 103 each recite SEQ ID NO:120 and should therefore not be subject to this rejection.

Turning to the merits of the rejection, the Final Office Action sets out several assertions which it contends supports the written description rejection. Each of these assertions purports to address the scope of the recited genus of polynucleotides having at least 90% identity to the full-length of SEQ ID NO:120. First, the Final Office Action asserts that "[t]he number of variant polynucleotide and amino acid sequences encompassed by the claim language is clearly beyond the scope of reasonable experimentation." Page 5, lines 17-20. Applicants disagree with this assertion as a matter of scientific fact. Even if it were true, what is within the scope of reasonable experimentation is an enablement standard. Enablement, as acknowledged on page 4

of the Final Office Action, is a separate issue from written description. There is no enablement rejection of the pending claims.

Second, the Final Office Action asserts that "nothing in the disclosure leads the skilled artisan to any particular nucleotide or amino acid sequence." Page 6, lines 1-3. This assertion is not relevant to the invention as claimed. Except for SEQ ID NO:120, which the specification discloses, the claims do not recite "any particular nucleotide or amino acid sequence."

Third, the Final Office Action contends that "the art is highly unpredictable and the skilled artisan cannot predict *a priori* the effects of any given substitution on the immunologic properties of the Env polypeptide." Page 6, lines 10-13. This assertion, too, is largely relevant to enablement, not written description. To the extent it is relevant, however, both the state of the art with respect to Env immunogenicity and computer analysis of Applicants' SEQ ID NO:120 show that the likelihood that an Env polypeptide within the recited genus will contain no immunogenic peptides is vanishingly small.

For example, Exhibit 1 is a Kolaskar[1] analysis of immunogenicity, which demonstrates antigens in the Env polypeptide encoded by SEQ ID NO:120. The peaks distributed across the entire length of the polypeptide show that multiple regions of the polypeptide contain discrete peptides, each of which can stimulate an immune response. In fact, the Kolaskar analysis actually underestimates the number of antigenic regions. Comparing the computer-based analysis to actual immunogenicity data, Kolaskar showed that the analysis identified 122 antigenic determinants out of 169 experimentally known antigenic determinants. Page 173, col. 2 ¶ 1. Thus, the Env polypeptide encoded by SEQ ID NO: 120 likely contains even more

[1] Kolaskar *et al.*, "A semi-empirical method for prediction of antigenic determinants on protein antigens." FEBS Lett. (1990) 276:172-4. A copy is enclosed with the accompanying Information Disclosure Statement.

antigenic determinants than is suggested by the computer analysis in Exhibit 1. Immunogenicity does not require that all these epitopes are present in the polypeptide; any one could suffice to stimulate an immune response.

Even a non-conservative alteration in a given polypeptide need not decrease immunogenicity; in fact, such an alteration may result in the formation of new immunogenic regions. Thus, rather than rendering Env unable to induce an immune response, changing the Env structure can create Env peptides with increased immunogenicity. Barnett,[2] for example, found that partial deletion of the V2 region improved immunogenicity to the Env protein as a whole and describes similarly enhanced immune responses obtained by others in the field:

> Wyatt *et al*. demonstrated that on the background of the HXB2 virus, a laboratory-adapted CXCR4-using (X4-using) virus, deletions of the first, second, and third hypervariable regions (V1, V2, and V3 loops, respectively) of the gp120 envelope subunit increase the exposure of epitopes participating in HIV envelope-CD4 and –coreceptor binding. Subsequently, it was demonstrated that the simultaneous deletion of the V1 and V2 loops from the envelope of this virus increases it susceptibility to neutralization by anti-V3 loop and certain CD4-induced monoclonal antibodies (MAbs).

Barnett, page 5536, paragraph spanning column 1 and 2 (citations omitted).

Furthermore, even when altering the Env polypeptide's sequence affects the type of the immune response generated, immune responses can still occur. Lee[3] showed that a single point mutation in the V3 region altered the secondary structure by removing a β-turn and decreased the

[2] Barnett *et al*., "The ability of an oligomeric human immunodeficiency virus type 1 (HIV-1) envelope antigen to elicit neutralizing antibodies against primary HIV-1 isolates is improved following partial deletion of the second hypervariable region," J Virol. 2001 Jun;75(12):5526-40, cited in the accompanying Information Disclosure Statement.

[3] Lee *et al*., "A single point mutation in HIV-1 V3 loop alters the immunogenic properties of rgp120," Arch Virol. 2000;145(10):2087-103, cited in the accompanying Information Disclosure Statement.

ability of the region to stimulate antibody production to that region; however, the ability of the mutated protein to stimulate a cell-mediate immune response was enhanced two-fold:

> Although unable to generate high titers of V3 loop antibodies, immunization of mice with the β-turn deficient clone D-UG23c was shown to promote an albeit moderate, but at least 2 fold increase in CMI [cell-mediated immunity] response when tested in a proliferation assay.

Lee, page 2100, paragraph spanning pages 2099 to 2100.

Others in the field have demonstrated that non-mutated full length Env polypeptides are highly divergent yet remain immunogenic. Chang[4] showed that the Env from divergent HIV isolates induces antibody formation. The Env sequences from HIV types A-J are 20% divergent; *i.e.*, the Env proteins from types A-J share only 80% identity.[5] Chang, page 442, col. 1, ¶ 1. Despite this divergence, the Env polypeptides stimulate immune responses. Chang found that "the distribution of highly immunogenic epitopes in the subtype E envelope is similar to the distribution previously observed in the subtype B envelope, although some differences in seroreactivity were noticed." Page 448, col. 2, ¶ 1. Thus, there is no basis for the assertion that immunogenicity of the recited Env polypeptides is so variable as to preclude adequate written description.

Fourth, the Final Office Action asserts that "the case law suggests that applicants must provide more than one or two examples to put them in possession of a large genus." Page 6, lines 13-15. It is black letter law that a specification adequately describes a claimed invention if it conveys to those skilled in the art that the applicants possessed the claimed subject matter

[4] Chang *et al.*, "Human immunodeficiency virus type 1 subtype E envelope recombinant peptides containing naturally immunogenic epitopes," J Infect Dis. 2000 Aug;182(2):442-50.

[5] The pending application is directed to Env sequences from HIV type C.

when the specification was filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). The fact that a claim encompasses a large genus exemplified by a small number of examples does not establish an inadequate written description.

The Final Office Action cites *Ex parte Kubin*, 83 U.S.P.Q.2d 1410 (Bd. Pat. App. & Int. 2007), *aff'd In re Marek Z. Kubin and Raymond G. Goodwin*, No. 08-1184 (Fed. Cir. 2009) (but not addressing the written description rejection) to support the assertion that the present claims are not adequately described. *Kubin* is not relevant because the claims at issue in *Kubin* are qualitatively different from the claims pending here. The *Kubin* claims recited a genus of molecules with a binding function. Binding function, like enzymatic function, could be affected by a single amino acid alteration. In contrast, Applicants' claimed subject matter is directed to polynucleotides encoding Env polypeptides that stimulate an immune response. An immune response to an Env polypeptide falling within the claimed genus can be generated by a single immunogenic peptide along the entire length of the peptide. There is no catalytic or binding activity that could be ablated by a single amino acid mutation. Nor is there even a necessary tertiary structure that mutation could destroy. Rather, there is only a requirement that the polypeptide induce an immune response. For the claimed polypeptides to lack the ability to stimulate an immune response, altering up to 10% of the amino acids would have to eliminate all immunogenic regions of the Env polypeptide encoded by SEQ ID NO:120 and not create any new immunogenic regions within the polypeptide. As discussed above, scientific evidence does not support this outcome.

The correlation between the claimed function and the effect of amino acid alterations is recognized in the Written Description Training Materials:

> [T]hose of skill in the art might require more or less correlating information depending on the kind of protein activity. If activity X is simply structural, e.g., a member of the collagen class, correlating information might not be a critical factor. However, if activity X is enzymatic, and there is no disclosure of the active site amino acids residues responsible for the catalytic activity, lack of that kind of correlating information may be a problem.

Training Materials at page 39.[6]

Whether the specification meets the written description requirement for the claimed invention is a question of fact. *Vas-Cath,* 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116. Using a computer, as supported by Example 11 of the Written Description Training Materials, the skilled artisan can readily envisage the sequence of each and every polynucleotide having at least 90% identity (or 95% or 99% identity) to SEQ ID NO:120. Substantial research into HIV Env protein immunogenicity has established that Env protein remains able to stimulate immune responses even when the sequences are mutated, have regions deleted, or are highly divergent. In view of these facts, there is no scientific or legal support for rejecting claims 38, 78-90, and 98-103 as inadequately described. Please withdraw the rejection.

Respectfully submitted,

BANNER & WITCOFF, LTD.

/Lisa M. Hemmendinger/

Date: April 8, 2009

By: _____
Lisa M. Hemmendinger
Registration No. 42,653

Customer Number 22907
202-824-3000

[6] The Final Office Action contends that the written description materials are guidelines and "may not be applicable to each and every application reviewed." Page 6, lines 26-27. The Final Office Action gives no reason why Example 11 does not apply to the present claims other than an assertion that "the sequence involved in the instant application is considerably larger than that provided in the training materials." Page 6, line 27 to page 7, line 1. Nothing in Example 11 of the Training Materials states the polynucleotide's size; thus, there is no way to compare whether the recited SEQ ID NO:120 is longer or shorter. Moreover, the length of a polynucleotide does not affect the ability of a computer to identify sequences which are 90%, 95%, or 99% identical to the polynucleotide.